REMARKS

The March 29, 2001 Official Action and the references cited therein have been carefully considered. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

In the March 29, 2001 Official Action, claims 1-14 and 17-20 have been rejected for allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph. It is the Examiner's position in this regard that because the present specification provides only a nucleic acid sequence and does not provide any sequences for the proteinaceous compounds of the claims, an adequate written description of the claimed invention is considered lacking.

Claims 1-14 have been further rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to provide a sufficiently enabling disclosure. It is the Examiner's position in this regard that undue experimentation would be required to practice the claimed invention.

In addition, various of the claims have been rejected on prior art grounds, as follows:

1. Claims 1-6, 11, 13, 17 and 18 are allegedly anticipated under 35 U.S.C. §102(e) by the disclosure of U.S. Patent No. 5,616,318 to Dudney;

2. Claims 1-5, 13, 17 and 18 are allegedly anticipated under 35 U.S.C. §102(b) by the disclosure of Gliniski and Jarosz in Comp. Biochem. Physiol., 85A (4): 673-77 (1986) (hereinafter "the Gliniski reference");

3. Claims 1-5 and 11-13 are allegedly anticipated under 35 U.S.C. §102(b) by the disclosure in published international patent application WO95/00647 of Smigeleski et al.;

4. Claims 1-3, 5, 6, 17 and 18 have been rejected as allegedly anticipated under 35 U.S.C. §102(a) by disclosure in applicants' present specification which is characterized by the Examiner as "admitted prior art"; and

5. Claims 7-10 and 14 are allegedly rendered obvious, under 35 U.S.C. §103(a) in view of the combined disclosures of the aforementioned Dudney, Gliniski et al. and Smigeleski et al. references in view of U.S. Patent 5,770,192 to Cayley et al.

The foregoing rejections constitute all of the grounds set forth in the March 29, 2001 Official Action for refusing the present application.

In accordance with the present amendments, the claims are now directed to proteinaceous toxins obtainable from a *Xenorhabdus nematophilus* species, which are either actually encoded by a specified sequence, or by one closely related thereto. The amended claims are fairly based on the application as originally filed, as indicated in the following table:

Correspondence between new claims and original claims:

New Claim No(s).	Original Claim No(s).
Claim 37	Claim 17 including features of original claim 1 (oral toxicity), claims 5 and 23
Claim 38	Claim 6
Claim 39	Claim 2
Claim 40	Claims 18 and 20, plus page 2, lines 17-21
Claim 41	Claims 1 or 32

Claims 42-49	Claims 7-14
Claim 50	New ("orally" has basis throughout the specification)
Claim 51	Claim 13 (as dependent on claims 4 and 6)
Claim 52	Claim 14
Claims 53-58	Claims 7-12

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

The various grounds of rejection set forth in the March 29, 2001 Official Action are clearly inapplicable to the new claims presented herewith. These grounds of rejection are, therefore, respectfully traversed.

A. Newly-Presented Claims 37-58 Fully Comply with the Written Description Requirement of 35 U.S.C. §112, First Paragraph

The relevant inquiry in determining compliance with the written description requirement of 35 U.S.C. §112, first paragraph, is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the claimed subject matter. In re Kaslow, 217 U.S.P.Q. 1089 (Fed. Cir. 1983).

Furthermore, the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in applicants' specification disclosure a description of the invention defined by the claims. Ex parte Sorenson, 3 U.S.P.Q.2d 1462 (Bd. Pat. App. 1987).

The lack of written description rejection cannot be maintained with respect to newly-presented claims 37-58. Such

a rejection is both legally and factually baseless as applied to applicants' new claims.

The legal insufficiency of the Examiner's position is clearly established by In re Fisher, 166 U.S.P.Q. 18 (C.C.P.A. 1970). In Fisher, the court held that determination of the amino acid sequence of a proteinase substance is not necessary, when the sequence is an inherent characteristic of a product disclosed in the specification. Applying this principle to the present case, it should be evident that by using conventional software analysis, the claimed proteins are inherently disclosed to one skilled in the art by the disclosed nucleic acid sequence.

Cases such as Fiers v. Revel, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993), which are cited in support of the Examiner's position, are readily distinguishable on the basis that isolation of a protein, in combination with a probing strategy for recovering the naturally occurring gene, may be insufficient to establish possession of a complete and operative embodiment of a later-claimed invention, where the claim is to a natural or human DNA sequence expressing the protein. Under such circumstances, possession of the protein itself is not sufficient positively to identify the structure of any natural DNA encoding for the protein, because of the large number of codons resulting from the degeneracy of the genetic code. Such is not the present case. In any event, none of the cases cited by the Examiner suggest that it is required that every claim sequence must be explicitedly disclosed.

The factual inadequacy of the Examiner's position is also clear, considering that in the present case, applicants

provide a reference sequence encoding demonstrated oral activity (seq. ID No. 1 from Clone 1 of NCIMB 40887-see Example 7-9), demonstrate that other sources containing closely related sequences (note the 11.4kb and 9kb fragments of NCIMB 40886 and ATCC 19061 discussed in Example 11) and that these organisms encode the same unexpected oral activity of sequence ID No. 1 (see Example 6-9).

Certainly, this is not a case of merely a "wish or plan" as stated by the court in Fiers.

For all of the foregoing reasons, it is clear that in the present case, the Examiner has failed to satisfy his burden of proof with respect to the lack of written description requirement rejection, as applied to the subject matter of new claims 37-58. Accordingly, this ground of rejection is untenable and should be withdrawn.

B. New Claims 37-58 Fully Comply with the Enablement Requirement of 35 U.S.C. §112, First Paragraph

Given that claim 17 was not rejected for insufficient enablement in the March 29, 2001 Official Action and that the subject matter of claim 17 is incorporated into new claim 37, it is presumed that applicants' new claims satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. To hold otherwise would be to grossly underestimate both the extent of the teaching of the specification and the level of skill in the art. The specification discloses not only methods of producing and using the claimed toxins directly from *Xenorhabdus* (see e.g. Examples I to 6), but also that the toxicity may be transferred to E. coli though Seq ID No I and retain the unexpected oral

toxicity (see Examples 7 to 9). This latter point directly contradicts the Examiner's comment (final paragraph Section 6) that toxicity may not even derive from a protein directly.

Regarding adaptation for oral activity, this term has been omitted from the claims. Thus, it is respectfully submitted that given the nucleic acid sequence (Seq. ID No 1), and the teaching in the Examples, there is clear correlation between the scope of applicants' new claims and the scope of enablement provided by the present specification, and there would not be undue experimentation for one skilled in the art to practice the invention as now claimed.

In summary, the rejection based on alleged lack of enablement, as set forth in the March 29 Official Action, is inapplicable to new claims 37-58, and should, therefore, be withdrawn.

Before addressing the specific grounds of prior art rejection set forth in the March 29, 2001 Official Action, a brief review of applicants' invention is presented below in order to point out those aspects of the invention which are believed to constitute patentable distinctions over the prior art.

The present invention relates to particular toxins derived from *Xenorhabdus nematophilus* which have oral pesticidal activity. The specification discloses that toxins of the invention are encoded by Seq ID No I (derived from NCIMB 40887 - see Example 9), and also that similar sequences are found in NCIMB 40886 and ATCC 19061 (see Example 11). In terms of sequence identity, encoded gene sequences in Seq ID No 1 appear to be quite different (less than 50% identity) with any previously

known toxin.

Additionally, no proteinaceous toxins previously known from *Xenorhabdus nemtophilus* had been demonstrated or suspected of having oral pesticidal activity, which activity is extremely important if the toxins are to be usefully exploited in the field.

In order to appreciate how unexpected the findings of the present inventors are, it is necessary to consider the technical background against which the invention was made. Nematodes present in soil seek out an insect host. They then puncture through the insect surface and release (i.e. effectively inject) *Xenorhabdus* bacteria into the insect's haemocoel. By evading the insect's immune system, producing antibiotics, enzymes and toxins, the insect is killed. The nematodes present in the insect also multiply, acquire *Xenorhabdus* bacteria and are released from the decaying carcass to find a fresh insect.

To study the infection process and in particular the role of the bacteria, enzymes and toxins in this process, the obvious experimental route is to mimic what the nematode does, but with each component separated. Therefore by injecting bacteria directly in to the insect's body in the absence of nematodes, the role they play in killing the insect can be determined. In addition, by injecting purified proteins, enzymes, toxins and antibiotics directly into the insects haemocoel the role these compounds play in killing the insect is also obtained.

Indeed there is a long and consistent history to this approach in the literature. One of the earliest papers reporting that *Xenorhabdus* kills insects upon entry and growth in the

haemocoel was published in 1966 by Poinar, G.A., and Thomas. G.M. (Parasitology. 56, 3853 90). Since then, numerous papers have been published confirming that *Xenorhabdus* kills insects once they are able to get into the haemocoel.

However over this thirty year timescale, up to the making of the present invention, there are no reports of high molecular weight proteins with oral activity from *Xenorhabdus.* Nor, in the light of the above, would the skilled person have expected such an activity - since in nature there is no reason why such toxins should have evolved to be able to kill the insect, without the assistance of a nematode to pass into the haemocoel.

Because the prior art of record fails to teach or suggest these unique aspects of applicants' invention, as briefly outlined above, the cited prior art does not provide a proper basis for rejecting applicants' claims, as the following discussion will clearly demonstrate.

C. The Prior Art Cited in Support of the Various §102 Rejections of the Original Claims Fails to Constitute Evidence of Lack of Novelty with Respect to the Subject Matter of New Claims 37-58

Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the reference cited as evidence of lack of novelty. In re Arkley, 172 U.S.P.Q. 524 (C.C.P.A. 1972). Applying this rule of law to the present case, the various 35 U.S.C. §102 rejections set forth in the March 29 Official Action cannot be maintained because the cited prior art fails to identically disclose the subject matter of applicants' newly-presented claims.

1. The Deficiencies in the Disclosure of the Dudney Reference

The Dudney reference relates to the use of X. *nematophilus* for the control of fire ants, to which the disclosure appears to be confined. This reference substantiates that the published literature, as of the priority date, suggested that *Xenorhabdus spp* were not considered to be orally acting. In any case the present claims recite methods of use of the specifically claimed proteinaceous toxins, or the use of specified cells, which are simply not disclosed in the Dudney reference.

2. The Deficiencies in the Glinski Reference

The Examiner appears to be reading more into this reference than is reasonably warranted, since it does not appear to show that significant mortality was caused by X. *nematophilus* when fed to the insects. Mortality was apparently only caused by injection of viable cells. The reference states at page 676 para 2 that X. *nematophilus* are effectively eliminated from the insect alimentary canal, indicating they are not having an effect upon the insect.

3. The Deficiencies in the Smigielski et al. Reference

Despite the comments with respect to plants etc. (which are standard claims for any patent application relating to nucleic acids) there is no evidence in Smigielski of a toxin which has oral activity. On the contrary, the only activity demonstrated in the Smigielski is by injection. Nor has the Examiner raised well-founded reasons to assume that the Smigielski toxins have oral activity. Certainly it is not sufficient to negate novelty merely because the Smigielski toxins

are purported to have certain activities which would be consistent with oral insecticide activity. The Smigielski toxin, which comes from a different X. *nematophilus* strain, does not appear to be related to the toxins of the present invention, for instance by way of homology or activity (e.g. in SDS). Nor does the Smigielski reference provide any reasonable basis for assuming that all *Xenorhabdus* strains will have oral activity. Indeed, as noted above in the introductory comments, the opposite is the case.

In assessing the patentability of the present invention insofar as the Dudney and Smegielski references are concerned, it is instructive to consider the International Preliminary Examination Report (copy attached) issued in the underlying PCT application. It is there stated that certain of the claims of the PCT application (which are directed to essentially the same subject matter as the new claims presented herewith) were deemed to satisfy all of the patentability criteria of the PCT. It necessarily follows that applicants' claims were determined to be patentably distinguishable over the Dudney and Smigielski references, which were included in the PCT International Search Report (copy enclosed).

4. Notwithstanding the Examiner's Assertion to the Contrary, Applicants Have Made No Admission of Prior Art that would Properly Support a Rejection Under 35 U.S.C. §102

The Examiner fails to cite, and applicants are unaware of any authority supporting the proposition that a deposit of biological material qualifies as prior art as of the date of its deposit. Although it is settled law that an applicant for patent may make a binding admission regarding prior art, provided that

the admitted prior art is labeled as such ("ipsissimis verbis"), with statements explaining same, as in In re Nomiya, 184 U.S.P.Q. 607, 611-12 (C.C.P.A. 1975), this is not such a case. Rather than admitting that NCIMB deposits 40886 and 40887 constitute prior art, the applicants herein expressly state, at page 4 of the present specification, that these strains are "novel" and "form a further aspect of the invention". Clearly, applicants have made no admission or concession that NCIMB deposits 40886 and 40887 constitute prior art in relation to the subject matter claimed in the present application.

In view of the above circumstances, unless the Examiner can support with sound legal authority his position that the deposit of biological material constitutes prior art as of the date of its deposit, the §102 rejection based on this alleged "admission" must be withdrawn. In this connection, the Examiner should consider the well-established principle that in the absence of a statutory bar under 35 U.S.C. §102(b), (c), or (d), an applicant's own invention cannot be prior art as to him. In re Fout, 213 U.S.P.Q. 532, 535 (C.C.P.A. 1982). Furthermore, it is believed that deposit of biological materials under the Budapest Treaty are not publically available under after patent publication, so that the deposit in question would not qualify as anticipatory prior art in this case in any event.

Inasmuch as none of the cited references, that properly qualify as prior art, identically disclose or describe all of the claim recitations of applicants' new claims, the various §102 rejections based on those references, as set forth in the March 29 Official Action, are untenable and should be withdrawn.

D. The Prior Art Cited in Support of the §103 Rejection of Applicants' Original Claims Fails to Render Obvious the Subject Matter of Applicants' New Claims 37-58

The Cayley reference plainly fails to supply the fundamental deficiencies in the prior art cited in support of the §102 rejections, as noted above. The Cayley reference merely suggests that *B.* thuringiensis toxins could be used in conjunction with other toxins, but it gives no specific guidance as to which ones. Certainly the Cayley reference does not suggest the specific X. nematophilus-based toxins or methods claimed in the present application. Therefore their use with *B.* thuringiensis can not be *prima facie* obvious.

So as to avoid any doubt on this issue, it should be noted that X. luminescent (mentioned at Column 5 of the Cayley reference) is a completely different organism from *Xnematophilus, and* belongs to a quite separate genus. Indeed a great deal of work has been done on investigating these differences which led ultimately to the renaming of X. luminescent to P. luminescent, based on DNA reassociation data; DNA relatedness; Phenotypic data; Chernotaxonomic data and Ribosomal RNA sequence analysis. Thus *Xenorhabdus forms* a distinct genus in which the different species show greater similarity to one another than they do to *Photorhabdus* luminescent, E coli, *Salmonella typhimurium* and other members of the enterobacteriacea. X *nematophilus is* as close to (or as distant from) E coli as it is P. *luminescent* and what may be obvious to try in one is certainly not obvious to try in another.

Even assuming that a *prima facie* case of obviousness has been established, which applicants vigorously dispute, it can

be rebutted by evidence of unexpected results. *(In re Merck & Co.*, 231 U.S.P.Q. 375, 380 (C.A.F.C. 1986)). The synergistic effect shown on page 18 of the present application is precisely such an unexpected result.

In summary, the §103 rejection based on the combined disclosures of the Dudney, Glinski, Smigielski and Cayley references, (with or without applicants' alleged admission of prior art) cannot properly be maintained with respect to applicants' new claims 37-58 and should, therefore, be withdrawn.

In view of the present amendments and the foregoing remarks, it is respectfully requested that the rejection set forth in the March 29, 2001 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

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Enclosures: Copy of International Preliminary Examination Report
Copy of International Search Report